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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/780,904	BUTLIN ET AL.	
	Examiner	Art Unit	
	Ginny Portner	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/9/05*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15,16 and 18-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *15 and 16* is/are allowed.

6)☒ Claim(s) *18-39* is/are rejected.

7)☒ Claim(s) *22,24,36-37* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 15-16, 18(amended)-32, 33(amended)-37 and new claims 38-39 are pending.

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 9, 2005 has been entered.

Allowable Subject Matter

1. Claims 15 and 16 define over the prior art of record and are therefore allowed.

Objections/Rejections Withdrawn

2. Claims 31-32 are no longer objected to for reciting the phrase "configured such that the such that when"; in light of Applicant's amendment deleting "the such that".

3. Claims 18-20, 33-37 rejected under 35 U.S.C. 102(b)as being anticipated by O'Daly et al (US Pat. 5,391,272), is herein withdrawn in light of the amendment of claim 18 to measure a single member of gonadotropin.

4. Claims 18-20,26-29 are rejected under 35 U.S.C. 102(b) as being anticipated by Overlie, I et al (1999), is herein withdrawn in light of the amendment of claim 18 to measure a single member of gonadotropin.

5. Claims 18, 26-27 are rejected under 35 U.S.C. 102(b)as being anticipated by Niccoli et al (1996) as evidenced by Costagliola et al (1994, reference 13, incorporated by reference), is herein withdrawn in light of the amendment of claim 18 to measure a single member of gonadotropin.

6. Claims 18,26-30 rejected under 35 U.S.C. 102(e) as being anticipated by Birken et al (US Pat. 6,521,416) is traversed on the grounds that Birken et al (US Pat. 6,521,416 is herein withdrawn in light of the claim amendments, but will be reformed into a new grounds of rejection.

Rejections/Objections Maintained

7. ***Claims Objection***: Claim 22 objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim, is herein maintained for reasons of record in paper number 08262004.

8. ***Claim Rejections - 35 USC § 112:*** claims 31-32 rejected under 35 USC 112, second paragraph for reciting the phrase "give rise to a similar indication" in claims 31-32 is a relative term which renders the claim indefinite.

Response to Arguments

9. Applicant's arguments filed November 9, 2005 have been fully considered but they are not persuasive.

Claim Objection Traversal

10. Applicant traverses the objection to claim 22 by asserting the Examiner is importing limitations into claim 21 that are not present in claim 21 by stating that inferential limitations may not be added to the claim.

11. It is the position of the Examiner that the phrase "combined alpha and beta chains of FSH" was defined by Applicant's own Specification at page 5 lines 32-33 that states "the alpha and beta peptide chains are the same in all FSH forms". The differences in FSH forms are defined in the instant Specification to be based upon "glycoforms (Instant Specification, page 5, line 25)". Claim 21 does not recite the term "glycoforms", nor "glycoprotein", but recites the phrase "alpha and beta chains of FSH" which are taught to be the same in all FSH based upon the two peptide chains (see page 5, line 18). The claims have been read in light of the definitions provided by the Instant Specification which permit the immunoassay of different peptide epitopes present on the alpha and beta subunits, as well as different carbohydrate epitopes on the alpha and beta subunits. Both antibody pairs that bind to both the alpha and beta subunits of FSH would measure Total FSH. No structural differences in the antibodies, nor any specific

epitopes have been so claimed to distinguish the antibody pairs in such a way that they would not bind total FSH. If the one or both of the antibody pairs of claim 21 is not to detect Total FSH, then the pairs should be so claimed based upon original descriptive support provided in the instant Specification. The second pair of antibodies that binds to the alpha and beta chains of FSH will also bind and detect total FSH, while binding with differing binding specificities, to a different combination of peptide epitopes. Applicant's traversal is not commensurate in scope with the instantly claimed invention as now claimed.

12. The alpha and beta chains present a plurality of peptide and conformational epitopes. Rose et al (2000) reviews FSH epitopes (see page 12, col. 2, paragraph 2) and states that the main antigenic epitopes of the subunits of FSH have been identified using a panel of 181 monoclonal antibodies. The alpha subunit was found to present at least 5 epitopes and two on the beta subunit, and an additional two which were conformational epitopes based upon the dimer-formed between the alpha-beta subunit. Bousfield et al (page 4, Figure 1, "hFSH") show human FSH to present both glycosylated and unglycosylated regions to which antibodies may bind. Glycosylation free regions of the peptide chains would present differing epitopes to which each of the first and second antibody pairs would bind. Therefore, the two antibody pairs set forth in claim 21, which bind to the alpha and beta chains of hFSH, would both measure total FSH in the sample.

If Applicant intends one of the pairs of antibodies recited in claim 21 not to bind total FSH based upon binding both the alpha and beta subunits, then this embodiment is not clearly set forth in the claims. While the specification can be used to provide definitive support, the claims are not read in a vacuum. Rather, the claim must be definite and complete in and of itself.

Limitations from the specification will not be read into the claims. The claims as they stand are incomplete and fail to provide adequate structural properties to allow for one to identify what is being claimed .

13. The objection to claims 22 under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim, is traversed on the grounds that the examiner's reading of the term "directing" in claim 21 to include the limitation "binding", and the term "directing" means simply that the have the potential to "bind" in some fashion, but not in the same way. Applicant asserts the antibody pairs of claim 21 "may recognize different regions of the same antigen".

14. It is the position of the Claim 21 does not require the antibody pairs to bind to different regions of the same antigen, but even if the antibodies did bind to different regions of the subunits of FSH, this does not preclude the antibodies from measuring total FSH in the sample. The members of each antibody pair of claim 21 are required to be different members and to bind to the alpha and beta subunits of FSH. In light of the knowledge in the art (see Rose et al above) that the alpha subunit presents at least 5 epitopes and the beta subunit presents at least two epitopes. Clearly two pair of antibodies with differing binding specificities would and could bind to different epitopes presented in the alpha and beta subunits and detect total FSH.

15. Additionally, the Examiner agrees that antibodies with differing binding specificities may bind to the same antigen, and in this instance, different epitopes presented by FSH, in different ways still detects Total FSH in the sample because total FSH is accomplished through detecting the combination of FSH alpha and beta chains through binding of one antibody to the alpha subunit and another antibody of the antibody pair to the beta subunit.

16. Applicant further traverses the objection to claim 22, by stating that " the application shows two specific antibodies, both of which were induced against the combination of alpha and beta chains, which have different binding specificity."

17. It is the position of the examiner that Applicant's traversal is not commensurate in scope with the instantly claimed invention of claims 21-22. Claim 21 does not claim any specific antibodies but generically claims the utilization of two antibody pairs in sandwich immunoassay formats to detect FSH, the FSH comprising both the alpha and beta subunits, the antibodies being directed against the alpha and beta chains of FSH. The first and second antibody pairs of claim 21 bind to the alpha and beta peptide chains would detect total FSH as does the antibody pair of claim 22 detect Total FSH. Claim 22 is not further limiting of claim 21 as now claimed because the binding specificities for the two pair of antibodies as claimed in claim 21, requires the first pair of antibodies to be different from the second pair of antibodies but both must bind to the "combined alpha and beta chains". Stating that first two antibodies are different from the second two antibodies does not define anything about their binding specificities other than they each bind to the alpha and beta subunits differently. Therefore, the two pairs of antibodies, while evidencing different binding specificities for the same FSH gonadotropin alpha and beta subunits, the two antibody pairs would bind to total FSH as total FSH is determined by measuring binding of the entire FSH molecule that contains both the alpha and beta chains in the claimed sandwich-format assay in claim 20, from which clams 21 and 22 depend. The rejection is maintained for reasons of record and responses set forth above.

18. ***Claim Rejections - 35 USC § 112:*** The rejection of claims 31-32 under 35 USC 112, second paragraph for reciting relative term: "give rise to a similar indication" rendering the claims indefinite is traversed on the grounds that "the Examiner is misreading the plain language of claim 18 and reading in limitations which are not present in claim 18." Applicant additionally asserts that claim 18, subparagraph b, never required that indications of the first and second assays be different and that the second assay only may vary depending on the menopausal status of the individual being tested and concludes that the comparison is carried out "relative to the indication the second assay may provide in another or the same individual in a different menopausal state. Such variation is not measured relative to any indication by the first assay."

19. It is the position of the examiner that the term "similar" by definition means a difference exists, as two things that are similar are not identical, but differ one from the other. The similarity between first and second assays may permit the results from the second assay to be higher or lower than the first assay, but how much of a difference is permitted to consider the assays as giving rise to a "similar indication" is not distinctly claimed.

20. Claim 31 also recites the phrase "discernibly different". Any measurable amount is discernible, but the amount recited in claim 31 is not required to be significantly different, albeit an increase or a decrease, as the amounts for a pre-menopausal state results in a similar indication and the post menopausal state is determined based upon any discernable difference from the first assay. An amount that is similar to the first assay and an amount that discernibly different to the first assay could be one in the same amount, because similarity does not require an identical measurement, and any discernible difference could be similar to the first assay. The American Heritage® Dictionary of the English Language: Fourth Edition. 2000 defines the term

" Similar" to mean Related in appearance or nature; alike though not identical. If the first and second assays are not identical, then they could be similar, and discernibly different from each other. The term "give rise to a similar indication" still is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably appraised of the scope of the invention.

21. What degree of similarity or discernible difference is being claimed that would differentiate between premenopausal and postmenopausal results set forth in claims 31-32 is not distinctly claimed. How a result can be similar, not identical, as well as discernibly different or not discernibly different at the same time is not clearly, nor distinctly claimed based upon the recitation of the relative term "similar indication" in the claims.

22. The examiner also notes that claim 31 does not require the comparison of the second assay results to be compared with "another" individual to determine menopausal status based upon the combination of claim limitations set forth in independent claim 18, from which claims 31-32 depend. Applicant's traversal is not commensurate in scope with the instantly claimed invention.

New Claim Limitations/New Grounds of Rejection

Claim Objections

23. Claims 24, 36 and 37 are objected to because of the following informalities:

a. Claim 24 does not end in a period, but a comma; the claim should be amended to be a complete sentence that ends in a period.

b. Claims 36 and 37 recite terms in italics "*reagent*" and "*zone*"; what this means is unclear. The italics should be removed. Appropriate correction is required.

Claim Rejections - 35 USC § 112

24. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

25. Claims 35-36 recite the limitation "detection zone of a labeled specific binding reagent with a particulate direct label" in modifying the device of claim 34, wherein claim 34 does not set forth the presence of a "labeled specific binding regent" nor does claim 34 define the presence of any zone or zones. Claim 34 recites the phrase "gonadotropin-responsive signal producing means", this means could be a labeled anti-antibody specific for an antibody that specifically binds to a gonadotropin family member. There is insufficient antecedent basis for this limitation in the claim 34 from which claims 35-36 depend.

26. Claims 37 recites the limitation "detection zone of a labeled specific binding reagent with a particulate direct label" in modifying the device of claim 33, wherein claim 33 does not set forth the presence of a "labeled specific binding regent" nor does claim 33 define the presence of any zone or zones. Claim 33 recites the phrase "gonadotropin-responsive signal producing means", this means could be a labeled anti-antibody specific for an antibody that specifically binds to a gonadotropin family member. There is insufficient antecedent basis for this limitation in the claim 33 from which claim 37 depends.

Claim Rejections - 35 USC § 102

27. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

28. Claims 18, 26, 31,38 are rejected under 35 U.S.C. 102(b) as being anticipated by Alfthan et al (1996).

Instant claim 18 and 38: Alfthan et al (1996) disclose the instantly claimed invention, the method comprising the steps of:

Obtaining a gonadotropin containing sample from a female individual (see section 7.3.2page 111, and page 112, serum samples, each individual sample is represented by the single data indicator "o".)

Performing contemporaneous first and second assays on the sample obtain in step (a) (see page 2, "hCGβ" just below hCG serum graph and hCG upper left frame under serum).

Wherein the first assay produces an indication independent of menopausal status (little change in serum concentration of "hCGβ" with increasing age);

Wherein the second assay produces and indication of a form of a gonadotropin that is dependent upon menopausal status (see hCG increases with age and menopausal status; also see

page 111, section 7.3.2, paragraph 1 "the concentrations of hCG in serum is dependent on age and menopausal status:.)

Instant claim 26: first and second sandwich format assays (see page 111, section 7.3.2, paragraph 1 "ultra sensitive immunometric assays with monoclonal antibodies"). At page 114, Figure 2, the immunometric assays is defined as a sandwich assay.

Instant claim 18 and 31: Comparing the results of the first and second assay to determine menopausal status of said individual (see page 111, col. 2, paragraph 4 "the median concentration of "hCGβ" is three to seven-fold lower than that of hCG and only a slight increase is observed with age").

29. Claims 18-19 and 38 are rejected under 35 U.S.C. 102(b) as being anticipated by Anobile et al (1998).

Anobile et al disclose a method the comprises the steps of:

(a) Obtaining a gonadotropin-containing sample (see page 632, col. 1, p3, serum samples aliquoted and frozen until needed for assay) from a female individual (see page 635, Fig. 3, "one woman") ;

(b) Performing contemporaneous first (LH bioassay, as well as pH determination on the sample to show charged isoform distribution; FSH concanavalin A affinity chromatography (see page 632, col. 2, p. 3-5) and second (LH and FSH immunoassay (see Delfia, col. 2, p 2), immunoassay "Delfia fluorescence immunoassay) assays on the sample from step (a); and

(c) comparing the results (see Figure 3, page 635, comparison made between immunoassay and pH assay of LH and FSH at various elution pHs to show charged isoform distribution) from the first and second assays to determine menopausal status, wherein the assays showed the presence and

distribution of human FSH and LH glycoforms in an individual that was still ovulating, and therefore was not menopausal, a pre-menopausal status (see page 634, col. 2, paragraph 2 and Figure 3). The reference anticipates the instantly claimed invention.

30. Claims 18-19 are rejected under 35 U.S.C. 102(b) as being anticipated by Ulloa-Aguirre, Alfredo et al (1995).

Ulloa-Aguirre, Alfredo et al discloses the instantly claimed invention directed to a method that comprises the steps of:

(a) Obtaining a sample from a female individual (see figure 2, page 768);

(b) performing contemporaneous first and second assays on the sample (see Figure 2, pH analysis (first assay), immunoreactivity assay (second assay) for FSH characterization of serum (see frame b "serum sample collected from a normal woman");

(c) comparing the results (the determined values for the first and second assays were compared in the graph shown in Figure 2, frame b, as well as compared with Metrodin, a commercial preparation of urinary FSH. Ulloa-Aguirre, Alfredo et al anticipates the instantly claimed invention as now claimed.

Ulloa-Aguirre, Alfredo et al also analyze urine and pituitary human samples (Figure 2) for the presence of, pH distribution, and immunoreactivity of human follicle-stimulating hormone isohormones (isoforms/glycoforms), and their physiological relevance (see title) based upon receptor binding assay (Figure 1, RRA, top graph), immunoreactivity within a hFSH assay for determining a quantitative amount of gonadotropin (see Figure 1, middle graph) and isoform distribution based upon one of three methods, the methods including separation by isoelectric

focusing (Figure 1, IEF, panel a), preparative chromatography focusing (Figure 1, CF, panel b) and zone electrophoresis (Figure 1, panel C), the separation methods identifying both more basic and more acidic forms of hFSH and hLH. The reference teaches less acidic isoforms of human FSH to evidence the ability to bind Concanavalin A, thus indicating the presence of greater proportions of high mannose and/or hybrid structures in these isoforms, wherein increased differential binding to Concanavalin A by human serum FSH depends on the physiological status of the individual, specifically the menopausal status of the individual (see page 769, col. 2, last paragraph) . Sera obtained from a postmenopausal individual would show greater proportions of FSH molecules binding to Concanavalin A than sera from normal menstruating women (see page 769, col. 2, last paragraph) is more acidic in nature would not bind to concanavalin A.

Ulloa-Aguirre, Alfredo et al goes on to teach the presence of increased basic isoforms when post menopausal women have been treated with an GnRH antagonist, a type of hormone therapy, the antagonist serving to prevent increased levels of gonadotropin (see Figure 4, page 773), as well as ratios of biological activity to immunologically reactive FSH to be correlated with isoform acidity and clearance rate (see Table 2, page 770, bottom of page; figure 9, frame B). Ulloa-Aguirre, Alfredo et al anticipates the instantly claimed invention.

1. Since the Office does not have the facilities for examining and comparing applicant's protein with the protein of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594

2. Inherently the reference anticipates the now claimed invention. Atlas Powder Co. V IRECA, 51 USPQ2d 1943, (FED Cir. 1999) states Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art...However, the

> discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior arts functioning, does not render the old composition patentably new to the discoverer. The Court further held that Athis same reasoning holds true when it is not a property but an ingredient which is inherently contained in the prior art.

31. Claims 18, 26, 31-32 and 38 are rejected under 35 U.S.C. 102(e) as being anticipated by Birken et al (US Pat. 6,521,416 B1).

Birken et al disclose the instantly claimed invention directed to a method of testing a human female individual to determine menopausal status (evaluate the metabolism of hLH in premenopausal, perimenopausal and post-menopausal women and to distinguish between normal and abnormal physiological states, see col. 3, lines 19-22),

Instant claim 18, 38: the method comprising the steps of:

(a) obtaining a gonadotropin-containing sample from a human female individual (see col. 4, lines 38-39 "one or more consecutive urine specimens");

(b) performing contemporaneous first and second assays on said sample obtained in step (a), (see col. 8, Figures 15 A-C, two assays, the first being for hLH concentration (figure 15C) and the second being a different form of hLHBcf which is dependent upon menopausal status (see Figure 15 A (perimenopausal, col. 8, lines 26-43), the antibody being specific for a protein portion and a carbohydrate moiety (see col. 10, lines 33-35)).

(c) comparing the results of the first and second assays to determine the menopausal status of the individual. The results from the first and second assays were compared to define a pattern for premenopausal women (see col. 8, line 34).

wherein the human female individual is undergoing a course of hormone replacement therapy (see col. 5, lines 37-39; the sample is obtained from a female under going hormone replacement therapy).

Instant claim 26: the first and second assays are sandwich format assays (see hLHBcf: col. 4, lines 40-5151; hLH: two different IRMAs (see col. 6, lines 62-63), IRMA are sandwich assays; Figure 8; also col. 9, lines 50-55)).

Instant claim 31: wherein a first assay and the second assay were discernibly different from each other (see Figure 17 A-B and col. 8, lines 45-52 "no pattern match"; "typical postmenopausal concentrations of the hLHBcf"; col. 13, lines 50-56 differences in hLH and hLHBcf (increased 6X-7X))

Instant claim 32: wherein the indications produced are the formation of color (see col. 9, lines 64-67 "enzyme, dye" produce color indications in assays). Birken et al anticipates the instantly claimed invention as now claimed.

32. New Claim 39 is rejected under 35 U.S.C. 102(b)as being anticipated by O'Daly et al (US Pat. 5,391,272). Claim 39 does not require the forms to be different forms of the same gonadotropin, but two different forms of gonadotropin.

Instant claim 39: O'Daly et al disclose the instantly claimed invention directed to a device (see Example 7, Figures 12(FSH) and 13 (LH) sandwich format) , the device being configured to at least:

Receive a sample means for combining the signals produced (spectrophotometric assay (see col. 20, lines 37-38 and claims 20-47 (electrode surface));

Assay a first form of gonadotropin to produce a signal (a first gonadotropin-responsive signal producing means, that relative to a reference standard produces a signal indicative of the gonadotropin present in the sample that is independent of whether the human is pre-menopausal or post-menopausal (see col. 20, lines 25-59)); and

Assay a second form of gonadotropin to produce a signal (a second gonadotropin-responsive signal producing means, that relative to a reference standard produces a signal indicative of the gonadotropin present in the sample that is different depending on whether the human is pre-menopausal or post-menopausal (see col. 19, lines 25-68, and col. 20, lines 1-23).)

Wherein the signals produced are indicative of FSH (see "colloidal gold adsorbed anti-FSH (see claims 29-30) together with an "enzyme/antibody conjugate). O'Day anticipates the instantly claimed invention as now claimed.

Claim Rejections - 35 USC § 103

33. Claims (method)18-23, 24, 26-28, 29, 38; (device) 33-37 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Berger (1988) in view of EP 0736771 A1 (1995).

Berger et al teach the importance of measuring FSH levels in a human sample to determine the presence or absence of dysfunctions of the hypothalamic-pituitary-gonadal axis due to elevated or decreased FSH levels (see page 2351, col. 1, last paragraph) .

Berger et al formulated a device that would receive multiple samples, comprised multiple combinations of antibody pairs for human gonadotropin sample analysis, the antibodies being means for producing a detectable signal, the signal being produced by a protein enzyme, the protein being a type of particle/particulate signal producing means (see page 2356, multi-well

plates; direct label of second antibody, narrative of Figure 4, last three lines of paragraph), each well being in a multiple well plate, the plate being means for combining the signals produced for signal comparison, each well being detection zone means for the presence and amount of hFSH in the sample.

The antibody pairs were different monoclonal antibodies for measuring FSH, wherein the monoclonal antibodies were directed to different epitopes presented by hFSH on the alpha, the beta or the combination of alpha and beta subunits (see Figure 2, shows 5 antibodies directed to the alpha subunit and 2 monoclonal antibodies directed to the beta subunit) .

Berger et al's carried out a method with the device comprising the steps of:

(a) **Obtaining** a gonadotropin-containing sample (see page 2352, c. 2, p 1 and Figure 1, ledger narrative);

(b) **Performing** sample analysis with at least first and second contemporaneous 2- site sandwich immunoassays (see figure 4, frame C) with at least two pairs of antibodies which bind to different antigenic epitopes of hFSH;

Wherein the first hFSH assay of said gonadotropin family member provides an indication that is independent of the menopausal status (may be a one hFSH specific antibody assay directed to the beta subunit (see Frame A, Figure 4, B2 and B3 detect hFSH specifically, as well and Beta-hFSH; or may be an assay with two different antibodies, specifically antibodies formulated in hFSH in a sandwich format: one directed to the central domain of hFSH and the other to the beta subunit (see Figure 4, frames A and C, combination shown: B2-C2; provides an indication of a form that does not correlate with menopausal status in light of the fact that the monoclonal c2 immunoreacts with both hFSh and TSH , wherein C2 reacts with an epitope held in common with hFSH and TSH (see Figure 4, Frame A, MCA c2 binding specificity) or could be the combination of B2-c1 or B3-c1 which would bind the central domain and the beta subunit) and

wherein the second assay provides an indication of a form dependent on menopausal status (the second assay measured both the α and β subunits of hFSH, thus measuring total hFSH in the sample (see Figure 4, page 2356, α3-β2; α3-β3; α5-β2; α3-c1; α5-c1); and

(c) **Comparing** the first and second assays for the ability of the antibody pairs (Berger et al evaluated and compared the assays for the different combinations of antibodies ability to detect the holo-hFSH glycoprotein in the sample (see p. 2356, IRMA for hFSH measurement, and Figure 4; Table 2, binding affinities of monoclonal antibodies).

Berger et al obtained a human biological sample that comprised a plurality of samples containing hFSH (Immunex lot of hFSH) and carried out first and second contemporaneous assays and compared the results from the assays

but differs from the instantly claimed invention by failing to show a biological sample obtained from an individual, the method to further comprise the step of obtaining a second sample after an interval of at least one week, and to teach the results to correlate with menopausal status.

Bartoli teaches a diagnostic device (see figure), formulated to carry out a sandwich format immunoassay (see col. 3, lines 53-57; col. 4, lines 19-21) with a gold particulate label signal producing means (see col. 3, lines 53-57) wherein the device is configured to determine menopausal status through measuring hFSH (see page 2, col. 2, lines 27-39) in first and second human samples (see page 3, col. 4, lines 11-21) obtained from an individual (woman, see abstract, front page), the second sample being obtained from the individual after at least one week (see col. 4, lines 54-57 "15 days") in an analogous art for the purpose of accurately (see title) detecting the menopausal status (see title, page 2, col. 2, lines 6-14) of the individual based upon hFSH, a clinical marker for diagnosing a woman with menopause (see title, figure, abstract) .

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the method of Berger et al with the biological samples of Bartoli because both references measure hFSH in a biological sample with sandwich format immunoassays and teach the importance of measuring hFSH as a marker for gonadal dysfunctions, and Bartoli teaches and shows hFSH to be a marker for determining the menopausal status of a female individual.

In the absence of a showing of unexpected results, the person of ordinary skill in the art would have been motivated by the reasonable expectation of success of testing a human female individual for menopausal status through carrying out the first and second immunoassays of Berger et al which utilize first and second pairs of antibodies that bind to different antigenic epitopes of the alpha and beta subunits of hFSH, on the first and second samples of Bartoli because both Berger et al and Bartoli successfully detected human hFSH in an biological sample utilizing a sandwich immunoassay format, and Berger et al produced and formulated a plurality of pairs of antibodies based upon differing binding specificities for the alpha and beta subunits of hFSH (see Berger et al Figure 2 and 4) and successfully produced first and second sandwich immunoassays for determining hFSH in a sample, wherein the sandwich immunoassays would readily detect the presence and amount of hFSH in the sample of Bartoli because Bartoli teaches and shows that hFSH is detectable in a human female individual sample based upon a sandwich immunoassay format who also teaches the importance of measuring hFSH in a second sample to insure that the detected level is not a normal level associated with menstrual cycle changes but is actually a positive result associated with menopausal status (see col. 4, lines 54-59 and col. 5,

lines 1-12). Berger et al in view of Bartoli obviate the instantly claimed invention as now claimed.

34. Claims 25 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Berger in view of Bartoli, as applied to claims 18-23, 24, 26-28, 29, 38; (device) 33-37 and 39 above, and further in view of Dullien (US Pat. 6,174,665).

See discussion of Berger in view of Bartoli above. Berger in view of Bartoli teach a method of determining the menopausal status of a female individual, but differs from the instantly claimed invention by failing to show the individual to be a female undergoing a course of hormone replacement therapy (HRT).

Dullien teaches and shows the measurement of hFSH in a sample (see col. 4, lines 13-17) obtained from female human individual undergoing hormone replacement therapy (see title, abstract, col. 4, lines 57-59) in an analogous art for the purpose of monitoring hormone replacement therapy for effectiveness in alleviating symptoms associated with menopausal status (see Dullien col. 3, lines 9-20).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the method of Berger in view of Bartoli with the sample of Dullien because Berger, Bartoli and Dullien all measure the presence and amount of hFSH in a human sample, and Dullien teaches the importance of measuring hFSH in a sample obtained from a human female undergoing a course of hormone replacement therapy (HRT) because Dullien teaches the importance of aggressively monitoring HRT therapy through assaying hFSH to insure the dosage of HRT administered is within the optimal range, the optimal range being

that range which will provide for the greatest effectiveness in releaving undesired symptoms associated with menopausal status, and if the dosage of HRT prescribed deviates from the optimal range a modified treatment dose can be determined(See Dullien, col. 4, lines 37-45).

The person of ordinary skill in the art would have been motivated by the reasonable expectation of success of assaying a human female individual undergoing HRT for the presence of hFSH to determine menopausal status in view of the guidance and teaching provided by Berger, Bartoli in view of Dullien because Dullien teaches the optimal ranges for FSH in blood, urine and saliva in a female individual undergoing hormone replacement therapy in order to assess menopausal status (see Dullien, col. 4, lines 55-63; and col. 3, lines 9-15).

In the absence of a showing of unexpected results, Berger, Bartoli in view of Dullien obviate the instantly claimed invention as now claimed.

Conclusion

This is a non-final action.

35. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

36. US005830680A is cited to show a multi-zone device for the determination of gonadotropins in a sample (see all figures).

37. US005981203A is cited to show a multi-zone device for the determination of gonadotropins in a sample (see all figures).

38. US005776785A is cited to show a device for the detection of analyte in a biological surface.

39. US 20050130311A1 is cited to show a method that determines menopausal status(see claims 1 and 26).

40. Berger et al (1996), Bousfield (1996), Burgon et al (1996) Cerpa-Poljak et al (1993), Charlesworth et al (1990), Green et al (1988, p 25-35) , Green et al (1988, p.36-44), Ho et al (1997), Rose et al (2000), Stanton et al (1992), Storring (1992), Vakharia et al (1990 and 1991), Vitt et al (1998), Weiner et al (1990 and 1992) are cited to show assay methods and reagents for determination of a gonadotrophin in a sample.

41. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (571) 272-0862. The examiner can normally be reached on M-F, alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vgp
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